

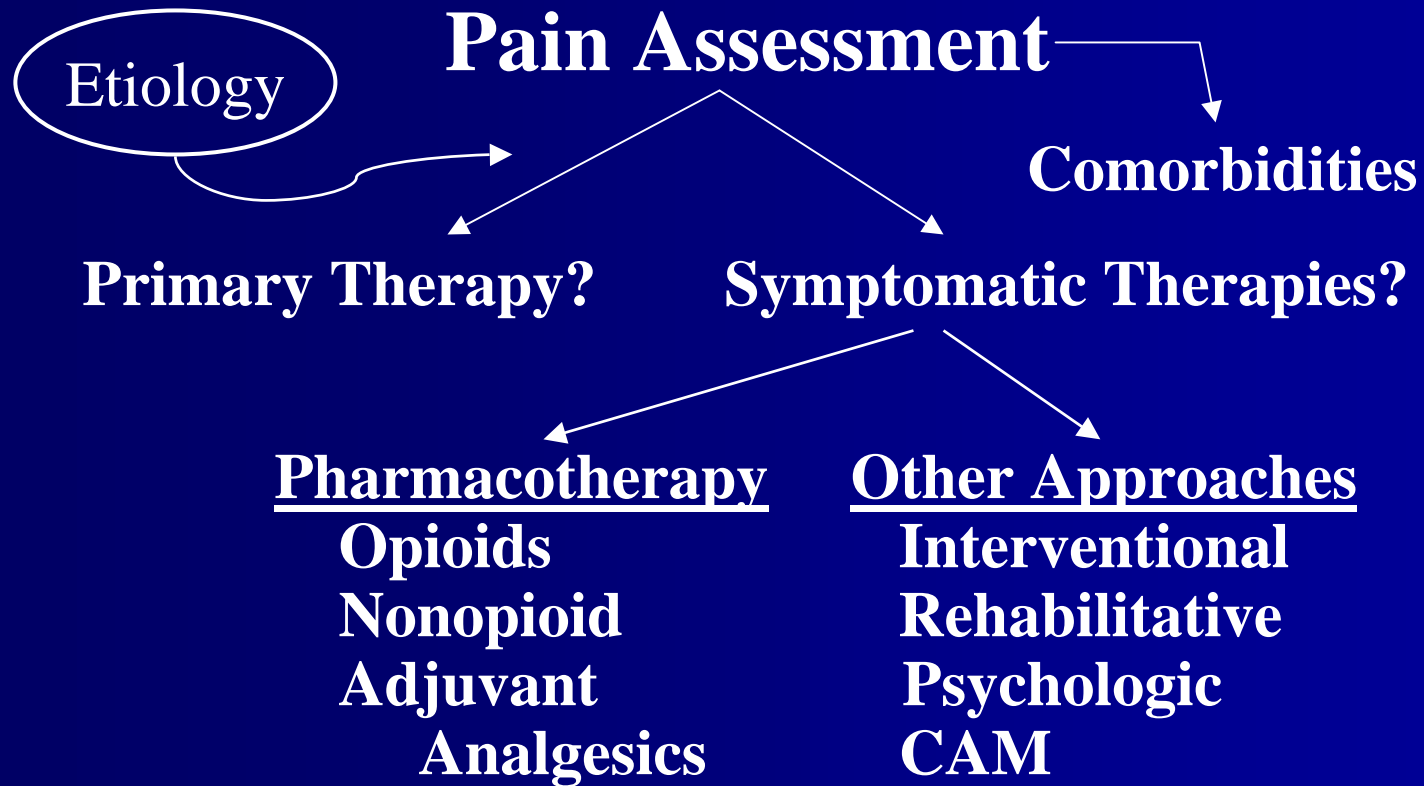
Adjuvant Analgesics

Russell K. Portenoy, MD

**Chairman and Gerald J. and Dorothy R. Friedman Chair
Department of Pain Medicine and Palliative Care
Beth Israel Medical Center**

**Professor of Neurology and Anesthesiology
Albert Einstein College of Medicine**

Approach to the Patient with Pain



Symptomatic Treatments

- Pharmacotherapy

- Rehabilitative approaches

- Psychological approaches

- Interventional approaches

- Neurostimulatory approaches

- Complementary and alternative approaches

Pharmacotherapy for Pain

Categories of Analgesic Drugs

- Adjuvant analgesics
- Nonopioid analgesics
- Opioid analgesics

Adjuvant Analgesics

- Traditional definition
 - Drugs with indications other than pain which may be analgesic in specific circumstances*
- Numerous drugs in diverse classes, some now specifically indicated for pain

Adjuvant Analgesics

- Multipurpose analgesics
- Drugs used for neuropathic pain
- Drugs used for musculoskeletal pain
- Drugs used for bone pain
- Drugs used for bowel obstruction
- Drugs used for muscle spasm

Adjuvant Analgesics

- Multipurpose analgesics
 - Based on number and types of studies
 - Classes
 - Corticosteroids
 - Antidepressants
 - Alpha-2 adrenergic agonists
 - Cannabinoids
 - Topical therapy: Lidocaine, capsaicin and others

Corticosteroids

- Consider analgesic use as distinct from use as disease-modifying agents
- Limited data on primary analgesic effects, but widely accepted in some disorders

Corticosteroids

- In advanced cancer and other advanced diseases, low dose regimen continued indefinitely for
 - neuropathic pain
 - bone pain
 - visceral pain
 - capsular pain
 - headache
 - Lymphedema
- Example: dexamethasone 1-2 mg BID

Corticosteroids

- In noncancer populations, short-term use accepted for
 - CRPS
 - carpal tunnel pain
 - severe vascular headache
- Not recommended for acute radiculopathy

Antidepressants

- Multipurpose analgesics
 - Numerous RCTs in diverse populations
(Sindrup et al, Basic Clin Pharmacol Toxicol, 96:399-409, 2005)
 - Consider for any type of chronic pain

Antidepressants

■ Classes

– Tricyclic antidepressants

- 3° amine drugs: amitriptyline, imipramine, doxepin
- 2° amine drugs: desipramine, nortriptyline

– SNRIs: duloxetine, minalcipran, venlafaxine, desvenlafaxine

– SSRIs: paroxetine, citalopram, others

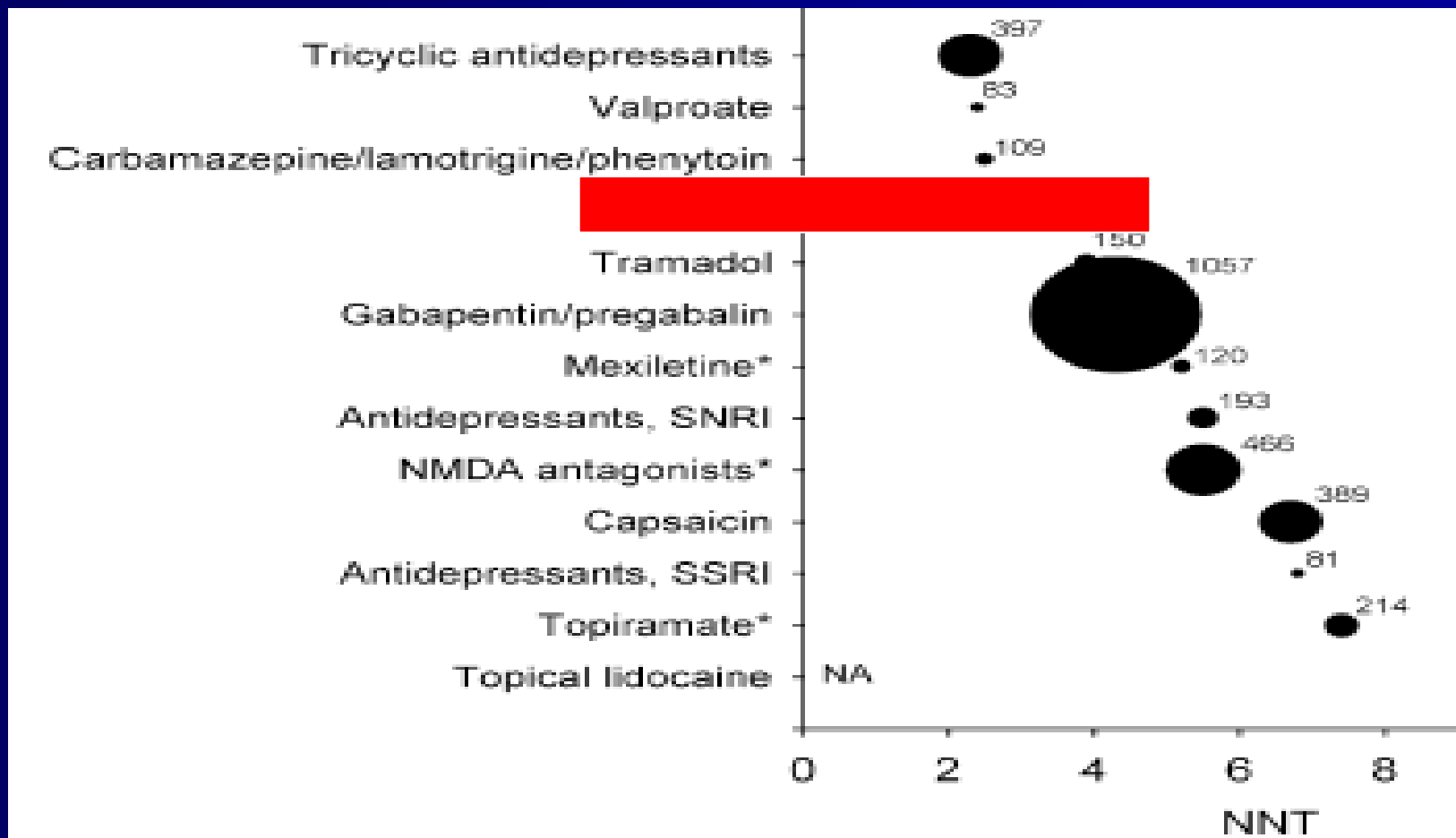
– Others: bupropion

Antidepressants

- Analgesic efficacy
 - TCAs > SNRIs > SSRIs
 - Of the tricyclics: 3^o amine drugs (amitriptyline) probably > 2^o amine drugs (imipramine)
 - Of the SSRIs, limited data in support of paroxetine and citalopram

Systematic Review: Treatments for Neuropathic Pain

Finnerup et al, Pain 2005;118:289-305



Antidepressants

- Side effects
 - 3° amine drugs > 2° amine drug > SNRIs/SSRIs/bupropion
 - CNS (both), anticholinergic (TCAs), CV (TCAs), nausea (SSRIs, SNRIs), sexual (SSRIs, SNRIs)

Antidepressants

- Based on safety and likelihood of efficacy, most reasonable choices would be 2° amine drugs or SNRIs
 - Desipramine
 - Nortriptyline
 - Duloxetine
 - Minalcipran
 - Venlafaxine

Antidepressants

- Desipramine
 - Starting dose 10-25 mg hs
 - Effective dose 50-150 mg hs or higher
- Duloxetine
 - Starting dose 20-30 mg daily
 - Effective dose 30 – 60 mg BID

α -2 Adrenergic Agonists

- Multipurpose analgesics but limited evidence
- RCTs support efficacy of clonidine, tizanidine and dexmedatomidine (Giovannani MP, et al, Med Res Rev 29:339, 2009)
- Tizanidine usually better tolerated than clonidine

α -2 Adrenergic Agonists

- Tizanidine
 - Nighttime dose can be hypnotic
 - Start with 1-2 mg hs
 - Effective range 2 – 20 mg BID

Cannabinoids

- Strong preclinical support for analgesic efficacy of both CB1 and CB2 agonists
- RCTs of THC in central pain (Svensen et al, BMJ, 329:253, 2004)
- Recent RCT of nabilone in fibromyalgia (Skrabek et al, J Pain 9:164, 2008)
- Recent positive RCTs of new formulation (THC plus cannabidiol) in central pain and in cancer pain (Berman et al, Pain, 112:299-306, 2004)

Cannabinoids

- Consider trial of THC or nabilone for refractory pain states
- Cannot endorse medical marijuana at this time

Topical Adjuvant Analgesics

- RCTs support benefit in neuropathic and arthropathic pain
 - Lidocaine 5% patch (Galer et al, *Pain*, 80:533-538, 1999)
 - Diclofenac patch (Brühlmann and Michel, *Clin Exp Rheumatol* 21:193, 2003)
 - Capsaicin (Ellison et al, *JCO*, 15:2974-2980, 1997)
 - Doxepin (McLeane, *Br J Clin Pharm*, 49:574-579, 2000)
 - Lidocaine gel 5% (Rowbotham et al, *Ann Neurol*, 37:246-253, 1995)
 - Aspirin (De Benedittis and Lorenzetti, *Pain*, 65:45-51, 1996)

Topical Adjuvant Analgesics

- Other topical compounds
 - Lidocaine/prilocaine cream (EMLA) and related formulations
 - Ketamine
 - Other antidepressants
 - Other NSAIDs
 - Various anticonvulsants
 - Opioids

Adjuvant Analgesics

- Drugs used for neuropathic pain
 - All multipurpose analgesics
 - Anticonvulsants
 - Others

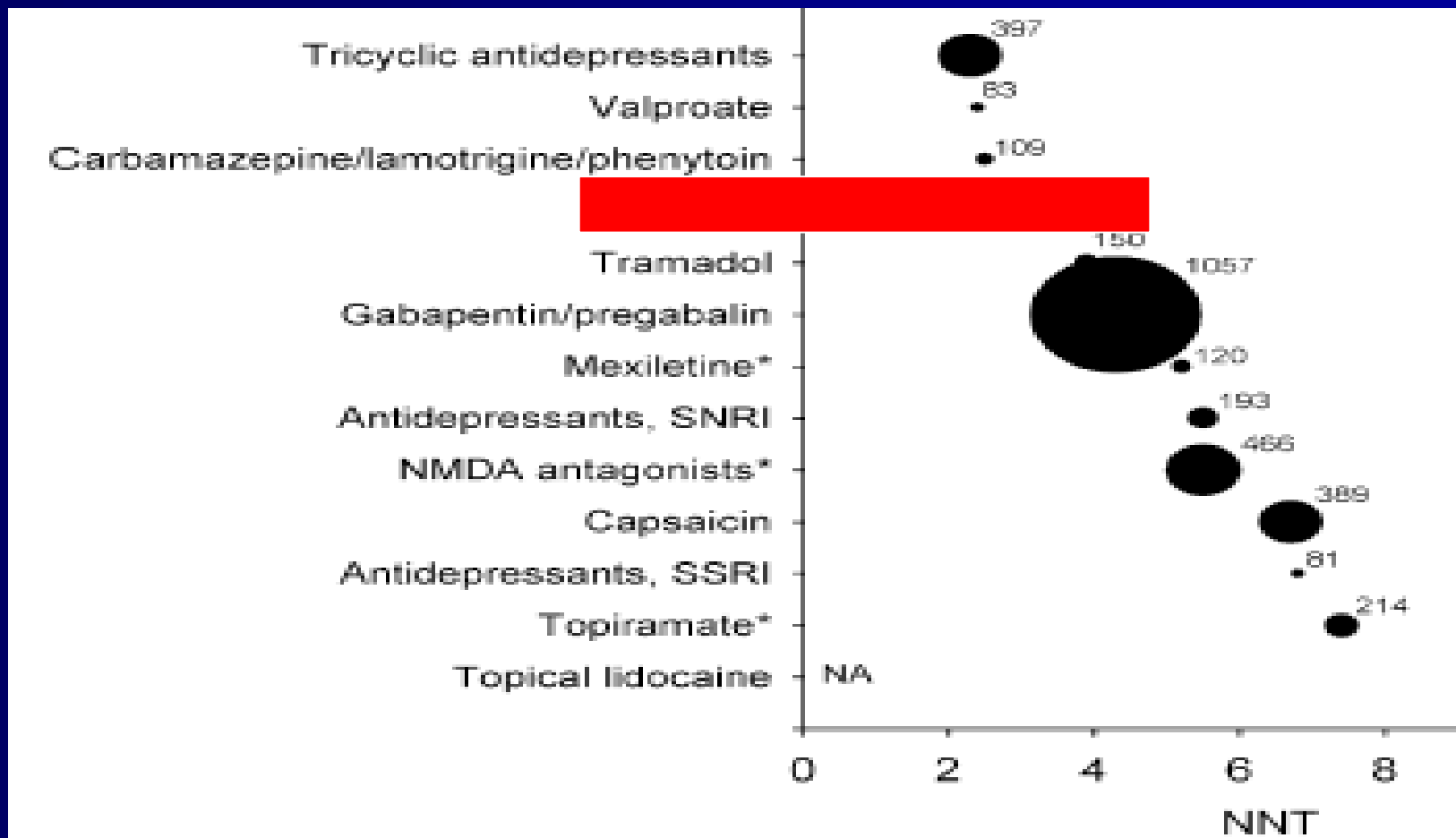
Anticonvulsants

■ Gabapentinoids

- Work via voltage-gated calcium channel, modulating alpha-2-delta protein
- Positive RCT's
 - Gabapentin: PHN/diabetic neuropathy, neuropathic cancer pain
 - Pregabalin: PHN/diabetic neuropathy/fibromyalgia
- NNT less favorable than TCAs, but first-line drug because of safety
 - Not hepatically metabolized
 - No drug-drug interactions
 - Side effects usually tolerable

Systematic Review: Treatments for Neuropathic Pain

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Anticonvulsants

- Gabapentin
 - Starting dose 100 – 300 mg qd
 - Effective dose 300 – 1200 TID or higher
- Pregabalin
 - Starting dose 25 – 75 mg qd
 - Effective dose 150 – 300 mg BID
 - Easier to titrate, faster onset
- May respond to one or the other, both or neither

Anticonvulsants

- Gabapentin and pregabalin
 - Adverse effects include somnolence, mental clouding, edema, weight gain

Anticonvulsants

- Other anticonvulsants have limited data and are selected by trial and error
- Older anticonvulsants with some evidence
 - ✓ Carbamazepine (trigeminal neuralgia)
 - ✓ Sodium divalproex (migraine)
 - ✓ Phenytoin

Anticonvulsants

- Newer anticonvulsants with some evidence
 - ✓ Topiramate
 - ✓ Oxcarbazepine
 - ✓ Lamotrigine
 - ✓ Lacosamide

Anticonvulsants

- Anticonvulsants with minimal to no evidence
 - ✓ Clonazepam
 - ✓ Levetiracetam
 - ✓ Zonisamide
 - ✓ Tiagabine

Anticonvulsants

- For neuropathic pain, evidence-based guidelines suggest gabapentinoid or antidepressant first
(Dworkin et al, Pain 5;132, 2007)
- Other anticonvulsants are for refractory pain: consider newer drugs first due to more favorable side effect profile

Sodium Channel Blockers

- Limited evidence that oral mexiletine, tocainide, flecainide are analgesic in neuropathic pain (e.g., Oskarsson P et al, Diabetes Care, 20:1594-1597, 1997)
- Efficacy of IV lidocaine supported by RCTs (Challapalli et al, Cochrane Database Sys Rev CD003345, 2005)
- Lacosamide is novel sodium channel modulator with limited evidence of efficacy in diabetic neuropathic pain (Wymer et al, Clin J Pain, 25:376, 2009)

Sodium Channel Blockers

- Side effects of conventional oral drugs common and usually considered for neuropathic pain after other drugs fail
- Role of lacosamide uncertain
- IV lidocaine is an option for severe neuropathic pain

NMDA-Receptor Antagonists

- NMDA receptor involved in neuropathic pain and opioid tolerance
- Commercially-available drugs
 - Ketamine
 - Memantine
 - Dextromethorphan
 - Amantadine

NMDA-Receptor Antagonists

- Ketamine

- 37 RCTs of ketamine plus opioids by single bolus or infusion show mixed but generally favorable results (Subramaniam K, Anesth Analg 2004;99:482-95)
- 4 RCTs of co-administration to opioids in cancer pain: no conclusion possible (Bell R, Cochrane Database Syst Rev. 2003;(1):CD003351)

- Dextromethorphan

- RCT of positive in DPN and negative in PHN (Nelson et al, Neurology, 48:1212, 1997)

- Memantine and amantadine

- Very limited positive data
- several negative RCTs of memantine

NMDA-Receptor Antagonists

- Conclusion: Limited data, conflicting findings
- Ketamine is useful in refractory pain

GABA agonists

- Baclofen
 - GABA-B receptor agonist
 - RCT in trigeminal neuralgia (Fromm et al, Ann Neurol, 15:240-244, 1984)
 - Intrathecal baclofen may relieve neuropathic pain apart from spasticity
- Tiagabine
 - GABA transporter-1 inhibitor approved for seizures
 - Limited evidence of efficacy
- Clonazepam
 - GABA-A agonist
 - Limited evidence of efficacy

Other Drugs for Neuropathic Pain

- Calcitonin
 - RCT's in RSD and phantom pain (e.g., Jaeger and Maier, Pain, 41:21-27, 1992)
 - limited experience
- Bisphosphonates
 - Positive observational data for pamidronate in RSD
 - RCT of clodronate in RSD (Varenna et al, J Rheumatol 27:1477-83, 2000)

Strategies for Neuropathic Pain

- Initial Strategy (Dworkin et al, Pain 5;132, 2007)
 - Treat etiology
 - Consider opioid if pain severe
 - Add gabapentin or pregabalin, if needed, unless comorbid depression is present
 - If comorbid depression is present, consider trial of desipramine, nortriptyline, duloxetine, or venlafaxine
 - Consider co-administered topical drug

Strategies for Neuropathic Pain

- Initial Strategy
 - If first-line drug unsatisfactory, consider sequential trials of adjuvant analgesics, starting with other antidepressants or anticonvulsants
 - Combination therapy is appropriate as long as each drug is demonstrably effective and tolerated

Adjuvant Analgesics for Musculoskeletal Pain

- **“Muscle relaxants”**
 - Numerous drugs, e.g., cyclobenzaprine, carisoprodol, orphenadrine, methocarbamol, chlorzoxazone, metaxalone
 - Centrally-acting analgesics
 - Do not relax skeletal muscle

Adjuvant Analgesics for Cancer Pain

■ For bone pain

- bisphosphonates (e.g. pamidronate)
- calcitonin
- radiopharmaceuticals
- (e.g. Sr^{89} , Sm^{153})

■ For bowel obstruction pain

- anticholinergics
- octreotide

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